Jerald Silverman, DVM, Column Coordinator

Clinical trial trouble

The College of Veterinary Medicine at Great Eastern University was participating in a clinical trial of Ostarest, a new chemotherapeutic drug with potential usefulness for dogs with osteosarcoma. Because the veterinary school was a recipient of grant dollars from the Public Health Service (PHS) and the University's Assurance with the federal Office of Laboratory Welfare (OLAW) covered all species used for research, the Great Eastern IACUC approved the clinical trial. The College's Clinical Trials Committee had also given approval. The instructions and disclosure notice, which was given to all dog owners who participated in the trial, required that the dogs be evaluated (and treated as necessary) at the veterinary college every 3 months at no cost to the owner.

Mr. Clyde, a 6-year-old bull mastiff, was part of the trial. His owner had recently obtained Mr. Clyde from an elderly relative who could no longer care for him. At the time of the first 3-month examination, the veterinarian noticed bruises on the same leg and in approximately the same area as Mr. Clyde's osteosarcoma. The veterinarian asked the owner some general questions, and the owner's responses raised no concerns. Radiographs indicated no progression of the disease or observable changes in the bone structure. The veterinarian recorded her findings in Mr. Clyde's clinical record. Upon examining Mr. Clyde 3 months later and noting more bruises, many in areas having no relationship to the tumor, she again ordered radiographs as well as blood samples. All findings were normal except for some inflammatory changes that did not seem to be related to the disease. Notably, none of the other 19 dogs in the clinical trial had any bruises similar to those seen on Mr. Clyde. The veterinarian began to wonder if Mr. Clyde was being abused. This suspicion grew considerably when Mr. Clyde was subsequently presented to the Great Eastern Veterinary Emergency Clinic with nasal bleeding and even more bruises. The owner demanded free treatment, claiming the problem was a result of the Ostarest trial. However, after a thorough examination and diagnostic tests, the Emergency Clinic and clinical trial veterinarians concurred that animal abuse, not the drug, seemed to be the problem.

The same day, the Great Eastern IACUC received the news that Mr. Clyde was most likely being abused by his owner. At an emergency joint meeting of the IACUC and the Clinical Trials Committee, called to discuss the matter, the Clinical Trials Committee claimed that the extent of its responsibility was to ensure that the trial itself was conducted properly. It had no responsibility for the owner's alleged actions. For its part, the IACUC said that it had no authority to interfere with actions that occurred in the home of an owner of a privately owned animal. The committees agreed to inform the authorities in charge of enforcing the state's animal anticruelty laws.

Did the IACUC have a responsibility to report its findings to OLAW and the Animal Care division of the federal Animal and Plant Health Inspection Service (APHIS/AC)? In retrospect, was there even a need for IACUC approval of a clinical trial with privately owned animals?

RESPONSE

Did the right thing

Lori R. Hill, DVM, DACLAM

This scenario raises several questions. Should the IACUC review these studies? Does the IACUC have jurisdiction over the owner and/or the dog? Should the College of Veterinary Medicine report the maltreatment to OLAW, USDA, and AAALAC International (if applicable)? Did the institution fulfill its responsibilities? Should policies be in place to address this situation?

An important consideration in determining if the IACUC must review these studies is the institution's Animal Welfare Assurance. PHS requires IACUC approval of PHS-funded activities as well as any other activities included in the Assurance[1]. Unless an institution can document that the animal program funded by a non-PHS source is entirely separate from PHS-supported activities, the OLAW will not consider its exclusion from the Assurance[2]. USDA regulations require IACUC review of activities involving covered species[3,4]. Individual funding agencies may require IACUC review and AAALAC accreditation. According to the National Research Council's *Guide for the Care and Use of Laboratory Animals* (*Guide*), AAALAC-accredited institutions would have to appoint an IACUC[5].

The next question is whether the institution has a responsibility for the dog while it is under the owner's control. The IACUC doesn't have the legal authority to compel the owner to participate in an investigation or to control the owner's behavior. OLAW considers the recipient of PHS funding to be the responsible party. If Great Eastern University's Assurance excludes activities not funded by PHS, then the institution is not technically responsible for this dog. USDA considers privately owned pets not to be regulated[6]. AAALAC's position is that responsibility for oversight follows ownership. However, during an AAALAC site visit officials could review client-owned animals housed at the institution and used in an approved protocol[7].

Should the IACUC report the abuse to OLAW and the USDA? The answer to this question is conditional. The PHS *Policy on*

Humane Care and Use of Laboratory Animals (PHS *Policy*) states "This Policy is applicable to all PHS-conducted or supported activities involving animals…[1]" If Great Eastern chose to include projects not funded by PHS in its Assurance, then it would seem that there is no choice other than to report the abuse to OLAW. If the Assurance doesn't include this project, then it would seem that the institution doesn't have to report. Because the USDA and AAALAC consider that responsibility follows ownership, there doesn't appear to be any requirement to report to these entities[6,7].

It seems that Great Eastern behaved ethically by informing the authorities. State and local laws define the institution's responsibilities to the animal. The American Veterinary Medical Association considers the veterinarian to be responsible for reporting such cases to the appropriate authorities[8]. According to the scenario, the dog received adequate veterinary care from Great Eastern's staff, and staff treated him humanely during his time at the institution. No protocol violation occurred. The IACUC fulfilled its obligation to investigate the animal welfare concern and determined that it could not pre-empt the rights of the owner.

The general conclusion is that there are no clearly defined guidelines in federal regulations or the *Guide* regarding the proper policies for this situation[9]. The IACUC should develop policies for conducting clinical trials that address the institution's methods for dealing with animal welfare issues and client-owned animals.

1. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.B.6; D.2 (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
2. Potkay, S., Garnett, N.L., Miller, J.G., Pond, C.L. & Doyle, D.J. Frequently asked questions about the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*. *Lab Anim. (NY)* **24(9)**, 24–26 (1995).
3. Animal Welfare Act as Amended (7 USC 2131–2159).
4. 9 CFR, Chapter 1, Subchapter A–Animal Welfare Parts 1–4.
5. Institute of Laboratory Animal Resources, National Research Council. *Guide for the Care and Use of Laboratory Animals* Ch. 1 (National Academy Press, Washington, DC, 1996).
6. Animal Welfare Act Summary, 2002. http://www.aphis.usda.gov/lpa/pubs/awact.html.
7. AAALAC Seminar at National AALAS 2005. Contracts, Collaborations and Co-Ownership: Rules and Responsibilities of the Institution.
8. AVMA Position Statement, Animal Abuse and Animal Neglect, 2005. http://www.avma.org/issues/policy/animal_welfare/abuse.asp.
9. Huerkamp, M.J. & Archer, D.R. in *The IACUC Handbook* (eds. Silverman, J., Suckow, M.A. & Murthy, S.) 14:28 (CRC Press, Boca Raton, FL, 2000).

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RESPONSE

Not responsible for reporting

Sonia D. Doss, BS, RLATG

The IACUC has a responsibility to review protocols for all projects involving the use of animals for teaching, testing, and research; therefore, IACUC approval was absolutely necessary for the Ostarest clinical trial. Although the IACUC cannot control which animals are accepted into the clinical trial, they should still review an example of the proposed consent form as part of the proposed protocol.

The consent form should clearly outline the purpose of the study and describe all procedures; moreover, it should identify and define the associated risks and benefits, potential costs to the pet owner, and obligations of the pet owner. It should also include information about withdrawing the animal from the study—by either the client or the veterinarian. The Principal Investigator (PI) and associated clinicians, the IACUC, the Clinical Trials Committee, and the University's Office of General Counsel should review the consent form.

Because Great Eastern receives funding from the PHS, the IACUC has the obligation to report its findings of abuse to OLAW under Section IV.F.3 of the PHS *Policy*; however, the scenario does not make clear whether the federal government funds the Ostarest clinical trial. If federal money is funding the clinical trial, then the report to OLAW must identify by name the PI and grant title, as well as any IACUC-required actions.

The Animal Welfare Act does not regulate clinical trials in client-owned animals; therefore, APHIS/AC would not receive notification of the findings, because the animal in question is a privately owned animal. Some members of the IACUC may feel a moral or ethical obligation to inform APHIS/AC of the situation; thus the IACUC should discuss and decide if they wish to provide a report to the USDA.

The Clinical Trials Committee is responsible for reviewing clinical trials conducted at the University. The Committee is also responsible for ensuring that the level of care for client-owned animals in clinical trials is the same as for other animals in their care.

Because the animals in the study are privately owned, the IACUC was correct in stating they did not have oversight responsibility for Mr. Clyde. The IACUC acted properly by informing the authorities responsible for enforcing the state's animal anticruelty laws. Because the examination and diagnostic tests confirmed animal abuse, the IACUC and/or the PI should immediately terminate the client's participation in the clinical trial in the best interests of the institution's animal care and use program.

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RESPONSE

Inform OLAW

Maggie McTighe, DVM

The Great Eastern IACUC has correctly reported the incident to the agencies responsible for enforcing the state's anticruelty laws[1]. They should also contact OLAW to discuss whether reporting is required. Regardless of the funding agency for this study, Great Eastern has a PHS Assurance, and adverse situations that may result in potential or actual affects on PHS-supported activities may result in a challenge of the functional or programmatic activities of Great Eastern[2]. The scenario also seems to imply that Great Eastern has extended its Assurance to cover all animal activities at the institution. Informing OLAW of the potential media coverage or legal actions of this disgruntled animal owner may help avoid adverse publicity that could jeopardize Great Eastern's program.

Although the ARENA/OLAW *Institutional Animal Care and Use Guidebook* does not

A word from USDA and OLAW

In response to the questions posed in this scenario, the United States Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (USDA, APHIS, AC) and the Office of Laboratory Animal Welfare (OLAW) offer the following clarification and guidance:

Abuse of a privately owned animal by the owner is outside the jurisdiction of USDA and of OLAW, even if the animal is on a PHS-supported study. The institution is obligated to report the abuse to the proper local or state authorities, and there are ethical and scientific reasons for removing the dog from the study.

Since the institution's Assurance covered all species used for research, OLAW would expect the IACUC to review the trial. USDA would expect likewise, if the clinical trial was conducted under funding from a Federal agency.

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Deputy Administrator

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Acting Director
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specifically address animal clinical trials, the following excerpt relating to farm animal studies, where animals are not necessarily housed at an institution, is relevant: "OLAW advises institutions that uniform and consistent standards are an essential ingredient in a quality animal care and use program. Public perception of a potential double standard should also be considered[1]." This reasoning seems to reinforce the reporting of this situation to OLAW.

Additionally, the study Director should confer with the University Counsel. An independent consultant may need to review the case.

Reporting the case to USDA is not necessary. A private individual owns this animal, and the University is not housing Mr. Clyde. Qualified medical personnel have determined that the injury to the animal is animal abuse, caused outside of the realm of the study and the institution. Reporting to the state's anti-cruelty authorities should be sufficient.

In retrospect, it would have been wise to have a thorough review of the clinical trials agreement by University Counsel/Compliance and Contract's Management before protocol review by the IACUC. This may help to clarify follow-up care more specifically and outline owner, institutional, commercial partner, and/or contractor responsibilities as applicable.

IACUC approval was necessary, because conduct of this study involves the institution's facilities, faculty, and staff members[3,4].

1. ARENA/OLAW. *Institutional Animal Care and Use Committee Guidebook* 2nd Edn. A.5; C.3 (2002). http://grants1.nih.gov/grants/olaw/GuideBook.pdf.
2. OLAW. NOT-OD-050034. Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Animals. (24 February 2005). http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html.
3. 9 CFR, Chapter 1, Subchapter A—Animal Welfare.
4. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* IV.B. 1–8 (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).

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